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Mini Review

Beyond Placebo: Alternative Options to the Randomized Control Trial Design in Rare Disease Studies

Preethi Sriram, DHSc, MSN, BSN, RN*

Clinical Research Professional, Morrisville, NC, USA

Corresponding author
Preethi Sriram, DHSc, MSN, BSN, RN
Clinical Research Professional, Morrisville, NC, USA; E-mail: srirampreethi@hotmail.com

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ABSTRACT

Unique difficulties and challenges can arise for rare diseases and orphan disease indications within a clinical trial. Some of the challenges encountered by trials that are working on rare diseases can include recruitment and enrollment. One of the explanations for the challenges that are encountered in rare disease trials is because of the trial design of study, where the investigational product is being compared to the placebo. This review paper discusses the usage of placebo and when other options could be taken into consideration while creating the protocol, specifically with consideration to rare disease studies. It is essential for the investigators and those designing the protocol to consider alternative options from the standard randomized controlled trial. The aim of this paper is to review alternative trial design options. The trial designs discussed in this review paper include crossover trials, single arm studies and historical data, and n-of-1 trials.

Keywords
Recruitment; Enrollment; Placebo controlled; Clinical trials; Rare disease; Crossover trials; Single arm study; Historical data; n-of-1 trials.

INTRODUCTION

Augustine et al[1] referenced in Orphan Drug Act that a rare disease is defined as affecting fewer than 200,000 people within the United States of America. Gaasterland et al[2] cited that while the European Union (EU) mentions a condition that is defined as rare is less than 2000 individuals, the authors mentioned that the total number of people who have a rare disease is larger i.e., it is estimated between 5000-7000 people. The authors also cited from the European Organization for Rare Diseases (EURORDIS), that is estimated up to 6-8% of the population of the EU have a rare disease. This demonstrates that while the particular number of people suffering from one rare disease may be low in numbers with regards to the definition from the European Union, the total number of people within the European Union suffering from a rare disease is large, when taking into account the number of rare diseases that exist, as well as considering the overall population suffering from a rare disease.

The Orphan Drug Act was passed by Congress in 1983 to handle the distinctive regulatory and commercial challenges brought about from orphan indications, and while the act was a success, there are 7000 known rare diseases without treatment.[3]

Augustine et al[1] discussed that there are many requirements for a study on human diseases, which includes the following; appropriate trial design and analysis, appropriate measurements to complement the design of the trial, proper participant selection, knowledgeable study personnel, as well as satisfactory funds to initiate and maintain the trial. The authors mention that when the study is for a rare disease, the constraints for studying a small group of patients can convert these obligations into great hurdles.

The obstacles encountered in rare disease studies for enrollment can also be significantly amplified if the study necessitates emergency care and critical care situations; this can be intensified yet another time if the protocol has strict time windows for enrolling and dosing the patient.[4] Some examples of emergency trials which can include cardiac arrest, seizures, trauma and injury, stroke, asthma, and other acute illnesses that debilitate the likely participant.[5]

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The following sections will discuss the highest quality level standards followed for of randomized controlled trials and potential alternative design options specifically for rare diseases with specific focus on crossover trials, single arm studies and historical data, and n-of-1 trials.

Trial Design

According to Portney and Watkins,[6] experimental designs give a base for comparing two or more conditions in order to determine cause and effect relationships, and the randomized controlled trial (RCT) is deemed the "gold standard" of experimental trials, where there is an experimental intervention and placebo. The authors discuss that RCTs have become an accepted way to determine whether an intervention has a significant impact on participants who receive the treatment in comparison to those who do not receive the treatment or placebo. The authors also discuss the concept of random assignment, which means that the participant in a clinical trial has equal probability of being assigned either to the intervention group or the control (placebo) group. The authors discuss that random assignment is an important aspect to experimental research, in that it provides the greatest confidence that no bias exists between the two groups.

This type of trial design is most utilized for common diseases and requires a large sample size and can be time consuming, and consequently may not be feasible method for rare disease trials; a small, uncontrolled trial may be an adequate alternative for a disease that is well understood with a consistent clinical course, and where the expected size of the effect is large.[1]

As the number of rare diseases is growing, the Food and Drug Administration (FDA) will be seeing more submissions with data from smaller clinical trials where the regulators will be in an uneasy role of having to determine safety and efficacy with less than ideal data.[3] The traditional gold standard for placebo-controlled studies necessitate investigators to divvy their sample population by half, and that because rare diseases are also deadly, potential participants are justifiably loathe to have to receive placebo.[3] There may be hesitation on the part of the parent, (which can extend potentially the participant or legally authorized representative) to enroll their child in a clinical trial where the participant may not receive the study drug, especially when there is progressing fatal disease, and thus a greater resolve on the part of the family to guarantee the participant is exposed to the active drug before the window of opportunity is gone.[1]

Regulations

As per the Nature article (2010), the FDA should allow for more flexibility in the design of the study[3] and this could be envisioned as a short placebo-controlled trial which then quickly moves into a trial that is open label, where both the patient and the investigator are aware of what is administered to the patient; in another example, it may even mean to abandon the placebo control.[3]

The FDA created a draft guidance in 2010 called "*Guidance for Industry – Adaptive Design Clinical Trials or Drugs and Biologics*" and Day et al[7] noted that the document gives advice on adjustments that can be prepared in a prospectively written protocol with regards to the inclusion criteria, procedures for randomization, total size of the population required, and endpoints. The authors remark that the FDA also encourages early intervention in order to help with evaluation of the drug, and note that better communication at various clinical stages raises the likelihood of positive clinical outcomes.

Suggestions

In rare disease studies, the gold standard for clinical trials may not always be feasible, and the protocol creators for the study should weigh the options of alternative trial designs such as review of historical data.[7] Other options that can be potentially considered include using a crossover design, using n-of-1 trials, or using adaptive designs.[8]

Three of the options discussed in this article are crossover trials, single arm studies and historical data, and n-of-1 trials.

Crossover Trial

While crossover trials can be used in various therapeutic indications, Wellek et al[9] noted that this design is used in high proportions within central nervous system (CNS) studies of neurology and psychiatry, and on trials for pain treatment. The authors mention that the main difference between a crossover trial and a conventional trial is that each participant is their own control. The crossover trial design thus avoids issues of comparability of the study and control groups, and can be beneficial in regard to the power of the statistical test carried out to confirm the presence of a treatment effect; the authors state that crossover trial needs smaller sample sizes in contrast to parallel-group studies in order to achieve the same requirements of risks involving statistical type I and II errors. It is remarked in the article that while utilizing this type of design, it is important to create the washout phase long enough to be able to concretely exclude any carryover effect from the treatment phase.

Single Arm Studies and Historical Data

Berry and Consultants[10] noted that the single arm study design is used in early phases of clinical trials such as phase 2 studies in oncology, and can also be appealing for rare disease studies, where subjects may be hard to locate and enroll, and may also be chosen when researchers determine that the treatment arms are no longer equally safe and effective. A condition for deciding to select a single arm trial is when the patient outcomes is well-known, where an example given by Berry and Consultants is the disease of Ebola, where there is high rate of mortality. Another example given are for diseases where the symptoms have a long duration, and there is no expectation for improvement without an intervention.

Berry and Consultants[11] stated that the control arm of a study rarely exists by itself and they may have been in several

studies pre-approval and post-approval, where data is available that gives information regarding the control arm that can be applied to the current study. If the prior studies are applicable, that information can be valuable and can eliminate possible biases and have more accurate estimates, and there would be a better of understanding of the control arm with the historical data. This could allow for potential elimination of some of the controls for the study, which thus would have the advantage of having quicker studies and more subjects on the treatment arm.

Some limitations of using this method is that if the source borrowed from is not appropriate, a bias can be created, which gives the possibility of decreased power, or increased statistical Type 1 error.[11]

Consequently, it is important for determining how to appropriately weight the prior studies.[11] For historical data, Berry and Consultants[11] describe the weighting system in detail, and state that the most common weights utilized are 0 to 1, where a 0 means that the previous historical data is not utilized, and 1 means that the previous data is equal in weight to the current subjects. The usage of 0 and 1 as a weight are two extremes, and usually the weighting falls somewhere in between 0 and 1.[11] In single arm trials, the weight can actually be greater than 1, where the treatment control arm is not present, and the only information available, is historical data. A heavier weight on historical data is suggested by Berry and Consultants[11] for prior studies that would be most applicable to the current study, while putting less weight on data that may not be applicable, would be prudent.

N-of-1 Trials

N-of-1 trials are clinical research designs that focus on the individual subject as the sole participant for the whole trial and the overarching aim of the study is to find the most ideal clinical treatment for the patient, while using data that is objective.[12]

An example where this study design was successfully utilized was a drug approved by the FDA for treatment of Batten disease.[13] The patient for the trial was an 8-year-old female who was diagnosed with a rare neurodegenerative disorder known as Batten disease where the patient had inherited a recessive mutated copy of the *CLN7* gene. The disease course is rapid and is ultimately fatal. In September of 2017, Dr. Timothy Yu and the team at Boston Children's Hospital (BCH) had created a drug for this indication and tested it on the cells of the patient, where the drug demonstrated efficacy.[13] The FDA granted permission to test the drug in January of 2018, one year after the team had started working with the family and the patient started to take the drug every 2-weeks for a total of 8-months through spinal injection.[13] After starting the drug, the patient has had a decrease in the frequency and duration of seizures and Dr. Yu and the mother of the patient have met with the FDA for exploring novel regulatory models for presenting antisense oligonucleotide therapies for those afflicted with rare conditions.[13]

CONCLUSION

Trials in rare diseases and orphan indications have unique challenges when it comes to recruitment and enrollment. Some of the challenges include having a low sample population for the trial, the potential subject or family/legally authorized representative hesitant to participating in the trial from chance of receiving placebo, or the trial time windows where enrollment is time sensitive, such as in critical care studies. In addition, a placebo arm to a study may not be ethical for certain diseases. When determining the type of study design, it is important to consider these factors. While a randomized controlled trial may be considered the gold standard for trial design, this type of design may not be optimal, or even ethical in certain clinical trials for certain orphan diseases or critical care trials. It is important for the investigators and those creating the protocol, therefore, to consider alternative options from the standard randomized controlled trial. This way, it may help to shorten the timeline from the pre-clinical phase to when the patient is able to get appropriate therapeutic treatment.

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